

## MRI-guided prostate adaptive radiotherapy – a review

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## Abstract

Dose escalated radiotherapy improves outcomes for men with prostate cancer. A plateau for benefit from dose escalation using EBRT may not have been reached for some patients with higher risk disease. The use of increasingly conformal techniques, such as step and shoot IMRT or more recently VMAT, has allowed treatment intensification to be achieved while minimizing associated increases in toxicity to surrounding normal structures. To support further safe dose escalation, the uncertainties in the treatment target position will need be minimised using optimal planning and image-guided radiotherapy (IGRT). In particular the increasing usage of profoundly hypo-fractionated stereotactic therapy is predicated on the ability to confidently direct treatment precisely to the intended target for the duration of each treatment.

This article reviews published studies on the influences of varies types of motion on daily prostate position and how these may be mitigated to improve IGRT in future. In particular the role that MRI has played in the generation of data is discussed and the potential role of the MR-linac in next-generation IGRT is discussed.

## MRI-guided prostate adaptive radiotherapy – a review

A consensus statement from the MR-linac consortium.

### Introduction

Randomised trials have demonstrated that dose escalated radiotherapy improves outcomes for men with prostate cancer [1]. The use of increasingly conformal techniques, such as step and shoot IMRT or more recently VMAT, has allowed this to be achieved while minimizing associated increases in toxicity to surrounding normal structures [2]. The accuracy of any radiotherapy delivery is however limited by multiple factors: organ delineation, set up error and inter-/intra-fraction organ motion, rotation and deformation [3]. A plateau for benefit from dose escalation using EBRT may not have been reached for some higher risk prostate cancers [4]. To allow further safe dose escalation, the uncertainties in the treatment target must be mitigated using optimal planning and image-guided radiotherapy (IGRT). In particular the increasing usage of profoundly hypo-fractionated stereotactic therapy is predicated on the ability to confidently direct treatment precisely to the intended target for the duration of each treatment [5].

Much work has been carried out over the past 20 years quantifying the degree of prostate motion, rotation and deformation that occurs during a course of radiotherapy, allowing rationalization of treatment margins based on expansion “recipes” [6]. The use of increasingly sophisticated real time imaging has enabled monitoring of the prostate and OAR’s through treatment delivery and has provided extensive data on their behaviour. MRI, with its unrivalled soft tissue delineation, has contributed to this data but has not, as yet, emerged as a routine part of daily radiotherapy delivery. The long anticipated arrival of a fully integrated MR-Linac may change this [7].

The ideal scenario is to guide prostate radiotherapy with MR imaging, identifying the prostate in real time while delivering radiation. Two systems (ViewRay and the Elekta MR Linac) hope to demonstrate improvement in patient outcomes with this technique.

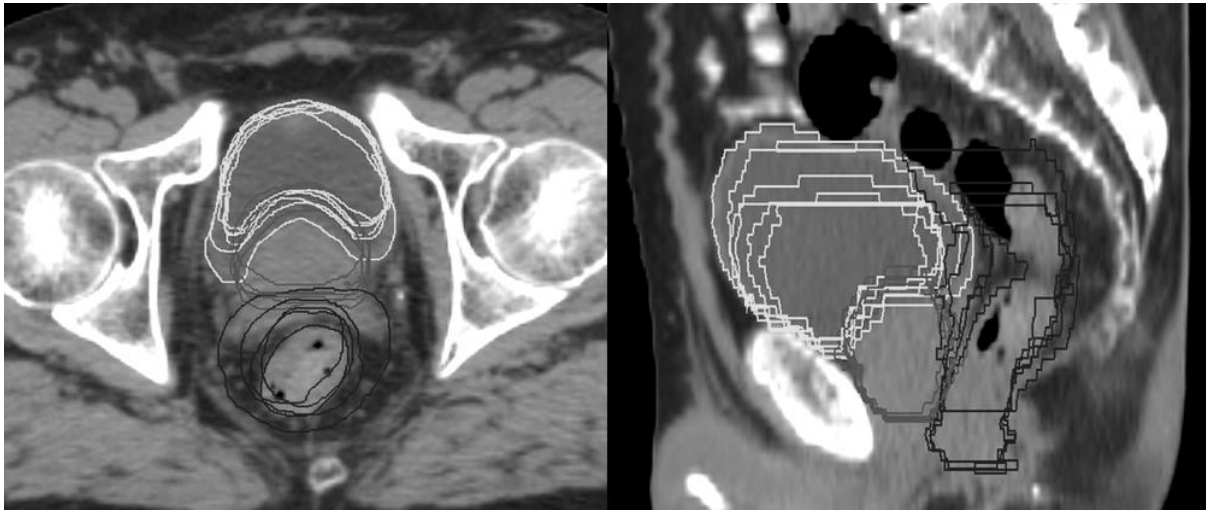
This article reviews data on target uncertainties when treating prostate cancer and in particular the work performed using MRI. Available techniques to reduce this uncertainty, and the potential benefits an MR-Linac may offer for IGRT are discussed. These data underpin the clinical work which will be undertaken on the MR-Linac to establish its utility in treating localized prostate cancer.

### Search strategy and selection criteria

References for this review were identified through PubMed with the search terms “prostate”, “adaptive”, “radiation”, “radiotherapy”, “motion”, “MRI”, “MR”. The literature review was performed between June and September 2015. References within identified papers were reviewed for relevance. A final reference list was generated on the basis of originality and relevance to the scope of this Review.

## Non-MR studies of inter- and intra-fractional prostate motion

The prostate experiences inter- and intra-fractional motion during a course of radiotherapy, as reported from an extensive body of work carried out over the past twenty years (**figure 1**). A comprehensive review of early studies indicates that the inter-fraction motion appears to have a standard deviation (SD) of around 1 – 4 mm, with one study finding motion with SD as high as 7.3 mm [8].



With increasing use of IMRT and consequently increased treatment duration, the significance of intra-fractional motion has grown, with appreciable variation being demonstrated [9-14]. A minority of patients experience more pronounced changes, as illustrated in a series of 427 patients assessed using fiducial markers (FM) and portal imaging, with motion > 3mm in 28% of treatment fractions over a ten minute period [15].

Multiple modalities been used to demonstrate that two general types of intra-fraction motion are seen: non-resolving slow drift, predominantly in the posterior direction due to rectal changes, and sudden transient motion, largely in the superior and anterior direction, likely a result of peristaltic visceral motion [9, 16-18]. Constant assessment also identifies greater intra-fraction motion; one study using Calypso 4-D tracking of 7738 records in 200 patients over 12 minutes showed the percentage of fractions with prostate shift >2, 3, 5, and 7 mm for > 30 seconds was 56.8%, 27.2%, 4.6% and 0.7% [19]. For the worst 10 patients, 5% of the total, these percentages increased to 91.3%, 72.4%, 36.3% and 6%.

Cohorts of patients assessed using multiple continuous imaging techniques have also found significant proportions experiencing movements >2-5mm, demonstrating the consistency of this finding within differing imaging modalities [20-23]. Intra-fraction motion has generally been found to be patient specific and predominantly random, although this has been challenged [24-26]. The observation that initial systematic intra-fraction changes can be predictive for subsequent movement may provide some guidance to likely behaviour during therapy [27-29].

Numerous studies have quantified the systematic and random components of inter- and intra-fraction motion to allow application of margin expansion formulas (Table 1 and 2).

Table 1: Inter-fraction systematic and random motion

Author	Pt no. (fractions analysed)	Imaging	Inter-fraction motion SD (mm)						Registration	Preparation
			Systematic motion			Random motion				
			AP	LR	SI	AP	LR	SI		
Zelefsky 1999[30]	50 (200)	CT	2.4	0.6	2.7	1.6	0.5	2.0	Bone	Prone, fleet enema at planning, empty bladder, immobilisation device
Stroom1999 [31]	15 (60)	CT	2.5	0.5	2.7	2.8	0.6	2.5	Bone	Foot and knee support Laxative prior to planning, 1 litre fluid 1 hour prior to scans
Hoogeman 2005 [32]	19 (209)	CT	2.7	0.3	2.1	2.4	0.4	2.1	Bone	Empty rectum, 250ml fluid 1 hour prior
Schallenkamp 2005 [13]	20 (798)	MV EPID + FM	2.5	2.0	1.9	3.5	1.6	2.0	Bone	Vacuum cradle
De Boer 2005 [33]	15 (255)	MV EPID + FM	2.1	0.8	2.0	1.9	0.7	1.2	Bone	Laxative prior to sim, full bladder
Litzenberg 2006 [34]	11 (-)	EM	1.5	2.2	3.0	5.2	3.4	3.3	Skin markers	Foot and knee support
Van den Heuvel 2006 [35]	10 (270)	MV EPID + FM	3.6	3.4	3.9	5.7	5.7	2.7	Skin markers	Alpha cradle
O'Daniel 2006 [36]	10 (243)	CT	3.9	1.6	3.4	3.6	2.5	2.0	Skin markers	Empty rectum, full bladder at simulation
Soete 2007 [37]	12 (120)	kV EPID + FM	4.3	1.3	4.2	2.8	1.6	2.3	Bone	Head and knee support
Van der Heide 2007 [38]	453 (15855)	MV EPID + FM	4.8	2.2	2.9	3.5	2.0	2.3	Skin markers	Knee, cushion. Bladder emptied 15 minutes prior to radiotherapy
McNair 2008 [39]	30 (408)	MV EPID + FM	2.5	1.3	1.9	3.1	2.2	2.2	Bone	Ankle/knee support, partially full bladder, empty rectum no prep
Beltran 2008 [40]	40 (1532)	MV EPID + FM	3.5	0.9	3.0	2.8	1.2	2.0	Bone	Not specified
Fiorino 2008 [41]	21 (522)	CBCT	0.3	0.2	0.2	1.0	0.6	0.7	Bone	Leg immobilisation, rectal enema + gas catheter, 250ml fluid 30 minutes prior
Byland 2008 [42]	24 (984)	CBCT	2.0	0.7	1.0	2.9	2.0	2.1	Mutual information algorithm	No bladder/bowel prep
Frank 2008 [43]	15 (369)	CT	4.1	0.9	2.9	1.3	0.5	0.6	Bone	Vac-loc bag, enema at sim, 590ml fluid 30 min prior
Mutanga 2008 [44]	10 (-)	MV/kV EPID	2.9	1.7	4.1	3.2	1.6	2.7	Skin markers	Not specified
Nijkamp 2008 [45]	20 (116)	CBCT	1.8	0.5	1.7	1.9	0.5	1.5	Bone	Empty rectum, 250ml fluid 1 hour prior, dietary advice
Tanyi 2010 [17]	14 (546)	EM	3.4	0.5	2.9	2.5	0.4	2.3	Bone	Not specified
Su 2011 [46]	17 (476)	EM	4.7	2.3	3.4	3.5	3.7	2.7	Skin markers	Not specified
Mayyas 2013 [47]	27 (1100)	BAT US	3.0	2.4	2.7	3.2	2.5	2.2	Skin markers	Empty rectum, partially full bladder
Oh 2014 [48]	17 (546)	kV EPID	3.4	2.6	3.1	2.9	2.4	2.0	Skin markers	Knee support, ERB, full bladder
Oehler 2014 [49]	20 (172)	CBCT	1.1	1.6	1.9	1.8	2.8	2.4	Skin markers	Leg immobilisation, empty rectum with ERB, empty bladder
		kV EPID	1.9	0.6	1.7	1.9	0.9	1.7	Bone	
		kV EPID	1.8	0.8	1.4	2.0	0.9	2.3	Bone	

CBCT, Cone Beam CT; FM, Fiducial Marker; EM, Electromagnetic transponder

Table 2: Intra-fraction systematic and random motion

Author	Pt no. (fractions analysed)	Imaging	Intra-fraction motion SD (mm)						Treatment time	Preparation
			Systematic motion			Random motion				
			AP	LR	SI	AP	LR	SI		
Beltran 2008 [40]	40 (1532)	MV EPID + FM	0.9	0.6	1.0	1.8	1.3	1.2	2 min	Not specified
Li 2013 [50]	105 (775)	EM	0.5	0.2	0.4	1.1	0.5	1.0	3 min	Not specified
Aubrey 2004 [10]	18 (282)	MV EPID + FM	0.7	0.2	0.4	1.4	0.8	1.0	<5 min	Full bladder, empty rectum
Li 2013 [50]	105 (775)	EM	0.6	0.3	0.5	1.2	0.5	1.1	5 min	Not specified
Choi 2015 [51]	12 (336)	kV EPID + FM	0.3	0.2	0.4	0.6	0.3	0.5	5 min	Ankle immobilisation, enema
Oehler 2014 [49]	20 (52)	CBCT + FM	1.4	0.9	1.4	1.6	1.0	1.4	3-6 min	Leg immobilisation, empty rectum with ERB, empty bladder
Kotte 2007 [15]	427 (11426)	MV EPID + FM	0.6	0.3	0.5	0.9	0.4	0.9	5-7 min	Knee support, empty rectum
Kron 2010 [26]	184 (5778)	kV EPID + FM	0.8	0.5	0.7	1.2	0.8	1.2	< 6 min	Not specified
Soete 2007 [37]	12 (120)	MV EPID + FM	0.8	1.3	1.1	1.6	1.4	2.4	7.5 min	Head and knee support
Kron 2010 [26]	184 (5778)	kV EPID + FM	0.9	0.6	0.8	1.2	0.8	1.1	6-9 min	Not specified
Su 2011[46]	17 (467)	EM	0.6	0.3	0.5	1.9	0.7	1.4	8 min	Not specified
Litzenberg 2006 [34]	11 (-)	EM	2.2	0.7	2.6	0.8	0.2	1.2	8 min	Ankle/knee support, no rectal/bladder prep
Tanyi 2010 [17]	14 (1638)	EM	0.5	0.3	0.7	1.4	0.8	1.3	8-16 min	Not specified
Kron 2010[26]	184 (5778)	kV EPID + FM	1.3	1.1	1.3	1.3	0.7	1.2	> 9 min	Not specified
Mutanga 2012 [27]	108 (2894)	MV EPID + FM	1.1	-	1.0	1.2	-	1.1	11 min	Headrest/knee support, void bladder 30 minutes prior, laxative at planning
Li 2009 [52]	105 (775)	EM	0.8	0.3	0.8	1.6	0.7	1.4	10-20 min	Not specified
Badakhshi 2013 [53]	13 (427)	kV EPID + FM	0.5	2.0	2.1	1.4	2.2	2.6	14.2 min	Empty rectum + full bladder, head and knee support, foot restraint
Mayyas2013 [47]	19 (-)	EM	1.3	0.6	1.5	2.6	1.4	2.4	20-30 min	Empty rectum, partially full bladder
Quon 2012 [28]	53 (265)	MV EPID + FM	1.4	0.2	1.2	2.4	1.3	2.0	Time not specified	Vac-loc bag, full bladder, empty rectum

CBCT, Cone Beam CT; EM, Electromagnetic transponder; EPID, Electronic portal imaging device; FM, Fiducial marker

## MR studies of inter and intra-fraction motion

The superb soft-tissue contrast and continuous imaging capability of MRI have allowed for confident assessment of inter- and intra- fraction prostate and OAR motion [54-65].

The first work with MRI to quantify prostatic motion used axial cine-MRI on 55 patients to evaluate intra-fraction motion of the rectum and prostate centre of mass every 10 seconds over a 6-7 minute period, representative of a radiotherapy treatment delivery time. This identified a median anterior shift of 4.2mm, which in 16% of patients was > 5 mm [54]. A subsequent study using sagittal and axial cine-MR over 9 minutes, sampling at 20 second intervals, for 42 patients identified displacement with SD 2.9mm, 1.5mm and 3.4mm in the AP, LR and SI plane [55]. The prostate was identified as tending to return to its original position after large displacements of up to 12 mm, motion which would be missed with pre and post treatment imaging alone [57]. This motion appeared to increase through the course of treatment, perhaps as a consequence of radiation induced toxicity

More recently intra-fraction prostate motion has been assessed by imaging 47 patients with prostate cancer after instructions to remove rectal gas [63]. Eleven points of interest were determined on axial and sagittal cine-MRI slices and monitored over a total of ten minutes. Displacement was more marked at the base of prostate than apex, likely a result of distal tethering, with mean of means SI and AP displacements of 0.41 mm and 0.86 mm for the former and 0.26 mm and 0.32 mm for the latter.

Continuous MRI has been able to demonstrate that intra-fraction motion increases with treatment time. A study using an open bore MR-scanner for a total of 68 sagittal cine-MRI sequences demonstrated an increasing displacement in the AP and SI planes during treatment with SD of 0.57 mm and 0.41 mm in the first two minutes increasing to 1.44 mm and 0.91 mm in minutes two to four [61]. This increase in motion appears to occur predominantly in the first few minutes of treatment with another study using cine-MRI imaging over 12-15 minutes finding motion at 3, 5, 10 and 15 minutes with an SD of 1mm, 1.3 mm, 2.1 mm and 1.9 mm in the AP plane and 0.7 mm, 1.8 mm, 1.5 mm and 1.6 mm in the SI plane [65].

The increasing intra-fractional motion seen initially over time shows the potential benefit of shortened treatments associated with VMAT compared to that with IMRT. Other studies using non-MR based imaging have also shown this increase and that it is the strongest predictor of observed displacements [18, 23, 26, 66-70]. These increasing movements can contribute 1-2mm to the required PTV margin [68, 71]. Shortened treatment times, such as those achievable by VMAT, have been shown to achieve a marked reduction in the SD of intra-fraction motion [19, 50, 66].

Stereotactic radiotherapy is challenging both due to the potential increase in treatment time compared to conventional VMAT and the implications of a geographical miss for even a single fraction. The necessity to avoid this obliges caution in margin reduction although it has been shown using Cyberknife that repeat imaging every 60 -180 seconds may be sufficient to allow correction for the increased prostate motion of longer treatments [72]. Even with regular repeat imaging 6-dimensional correction for rotation and translation is required if margins as small as 3mm are to be achievable.

## Deformation and rotation

Many studies of prostatic motion have assumed rigid motion of the prostate. Analyses of prostate changes have shown this to be a simplification although the degree of deformation identified has varied substantially. For example a study comparing the contoured prostate to an average CTV on 8-12 CT images for 19 patients matched for rotation and translation found “real” shape variation, correcting for inter-observer variation, of 1.6 mm at the SV tip and 0.9 mm at the posterior prostate [73]. Another group used three repeat CT scans with prostate and SV contoured and matched to a planning CT and non-rigidly registered to represent deformation [74]. Deformation of the prostate was small ( $\leq 1$  mm) while the deformation of SV was up to 2.6 mm SD posteriorly. More marked variation has been suggested; a study matching 200 cone beam CT (CBCT) images for ten patients to planning CT images using B-spline-based deformable registration identified a much larger deformation of the prostate, most marked in the anterior direction with a maximum of 10 mm, 5 mm and 3 mm in 1%, 17% and 76% of cases [75]. Again SV deformation was larger, with changes in the posterior direction of  $>5$  mm and  $>3$  mm in 7.5% and 44.9% of cases. For this analysis three clinicians delineated contours which were averaged in an attempt to reduce error however the SD of the mean centre of mass of the contours was up to 2.2 mm. It may therefore be that the inferior CBCT image quality, limiting contouring accuracy, contributed to the larger changes identified.

MRI, which may mitigate delineation errors associated with CT imaging, has also been used to assess deformation. A study of 10 patients using sagittal and axial cine MRI of the prostate to assess changes in the volume of contoured prostate over six minutes found similar results to those obtained using CT imaging with a deformation with a SD 1.7 mm in the AP plane shown [76]. Interestingly it has been suggested through tracking points of movement in sagittal MRI imaging that deformation is only seen with a full rectum, and is most marked at the level of mid-prostate [57].

The cause of deformation is due both to mass effect from surrounding structures and as a consequence of treatment itself with the prostate being shown to change in volume during radiotherapy. For example 25 patients underwent MR imaging pre-radiation and at one time point during therapy to assess prostate motion and deformation through treatment [58]. Scans were compared using finite element modelling aligned on the centroid of three FM. An increase in prostate volume by up to 34% was seen in those scanned early in treatment whilst a decrease of up to 24% was seen later in the course. The degree of shrinkage seen over a course of radiotherapy is affected by the use of neo-adjuvant hormone therapy and pre-treatment volume but may be generally of the order of 10-15% [77-80]. This has implications for further development of MR-guided radiotherapy, which can account for the intra-fraction motion described above, but would need further technical developments to adapt for deformation.

The effect of systematic and random inter-fraction rotations on prostate motion has been assessed by various groups using CT, kV and MVCT or EM imaging. These rotations predominate in the sagittal plane and appear to correlate with rectal filling; this moves the prostate in the AP direction, causing rotation due to apex tethering [81]. The differing bowel preparations employed by various groups may affect rectal volumes and contribute to the variation in degree of rotation identified.

Intra-fractional rotation has been less well characterised and although appearing smaller, it remains relevant (table 3). A study using continuous kV imaging with FM during the treatment of 10 patients with prostate cancer found for 35% of treatment time the prostate rotated more than  $5^\circ$  around the



lateral axis [82]. These intra-fraction rotations may be clinically significant. For example even with daily translations the intra-fraction rotation during RT can cause significant under-dosing, and margins of 3mm may be required to account for rotations of up to 5° [72, 83]. The significance of prostatic rotation is only likely to increase as treatment margins further reduce.

Table 3: Studies of intra- and inter-fraction rotation

Author	Pt no. (Fractions analysed)	Imaging	Inter-fraction rotation SD (degrees) around each axis						Registration	Preparation
			Systematic			Random				
			AP	LR	SI	AP	LR	SI		
Stroom 1999 [31]	15 (60)	CT	0.8	3.6	1.7	0.9	3.3	1.5	Chamfer match	Laxative prior to simulation. 500ml 1hr prior to imaging. Knee, foot, arm support
Dehnad 2003 [84]	10 (241)	CT + MV EPID + FM	2.0	4.7	2.7	1.7	3.6	1.9	Prostate COM	Knee support
Aubrey 2004 [10]	7 (348)	MV EPID + FM	2.2	5.6	2.4	2.0	6.1	2.8	Prostate COM	Full bladder, empty rectum
De Boer 2005[33]	15 (255)	MV EPID + FM	1.5	4.9	1.9	1.6	4.7	1.0	Bone	Laxative prior to simulation, full bladder
Hoogeman 2005 [32]	19 (209)	CT	1.3	5.1	2.2	1.6	3.6	2.0	Chamfer match	empty rectum
Van der Heide 2007 [38]	234 (8190)	MV EPID + FM	2.8	2.8	2.8	1.7	3.1	2.0	Prostate COM	Empty bladder, knee support
Mutanga 2007 [44]	10 (3382)	kV/MV EPID + FM	1.7	4.9	1.3	1.3	4.2	1.6	Prostate COM	Not specified
Nijkamp 2008 [45]	20 (128)	Weekly CBCT	0.9	2.9	1.0	1.0	3.0	1.1	Bone	Dietary advice, daily mild laxative, empty rectum, 250ml fluid 1 hr prior to imaging
Mutanga 2011 [85] (from van der Wielen[74])	21 (84)	CT + FM	2.0	4.3	2.2	1.2	4.5	1.8	Prostate COM	Laxative prior to simulation
Graf 2012 [86]	38 (969)	kV EPID + FM	1.6	4.1	2.3	2.0	3.1	1.8	Bone	Enema prior to simulation, empty rectum, bladder filling, head/knee support foot immobilization
Smeenk 2012 [87]	15 (576)	EM	2.9	10.2	7.0	1.3	3.9	1.5	EM	Knee support, foot immobilization

Author	Pt no. (Fractions analysed)	Imaging	Intra-fraction rotation SD (degrees) around each axis						Treatment time	Preparation
			Systematic			Random				
			AP	LR	SI	AP	LR	SI		
Aubry 2004 [10]	7 (44)	MV EPID + FM	0.3	1.0	0.8	0.6	1.8	1.1	<5 minutes	Full bladder, empty rectum
Badakhshi 2013 [53]	13 (427)	kV EPID + FM	2.3	2.2	2.4	2.5	5.1	3.5	14.2 minutes	Full bladder, enema., head and knee support, foot restraint

CBCT, Cone Beam CT; CMO, Centre of Mass; EPID, Electronic portal imaging device; FM, Fiducial Marker; EM, Electromagnetic transponder

## Relative motion of prostate and seminal vesicles

In high risk disease the likelihood of occult involvement of the SV is increased [88]. It is therefore generally necessary to include this area in the intended CTV for radiotherapy planning. The base of the SV is the region most likely to harbour occult disease, with one pathological series finding disease 2cm beyond this in only 1% of all patients [89]. This area must therefore be prioritised to receive the full prescribed dose. CT imaging has demonstrated that the SV tips undergo greater inter-fraction movement than the base and consequently larger expansion margins are required if it is clinically necessary to treat its entirety [90, 91].

It has been shown that the SV and prostate can behave independently making appropriate expansions to PTV challenging [49, 73, 92]. The SV volume may vary by as much as 100% during a course of radiotherapy and experience significant independent deformation [78, 92]. Inter-fraction SV motion appears more significant than that of the prostate gland with a SD in the order of 2.9 – 7.3 mm, 1.9 - 3.1 mm and 2.1 - 5.5 mm in the AP, LR and SI planes [30, 43, 79, 91, 93, 94]. Despite direct tumour invasion reducing SV mobility, this motion may remain considerable [95].

Allowing for intra-fractional motion is also problematic. Overall intra-fractional displacement of the SV appears greater than for the prostate and increases over time. In one series using cine-MRI it was found that for 95 % of the images SV centroid movement at 3, 5, 10 and 15 minutes was 4.7 mm, 5.8 mm, 6.5 mm and 7.2 mm respectively in the SI plane and 4.0 mm, 4.5 mm, 6.5 mm and 7.0 mm in the AP plane [65]. The correlation between prostate and SV intra-fraction movement was shown to vary greatly with no relationship between the two for most patients



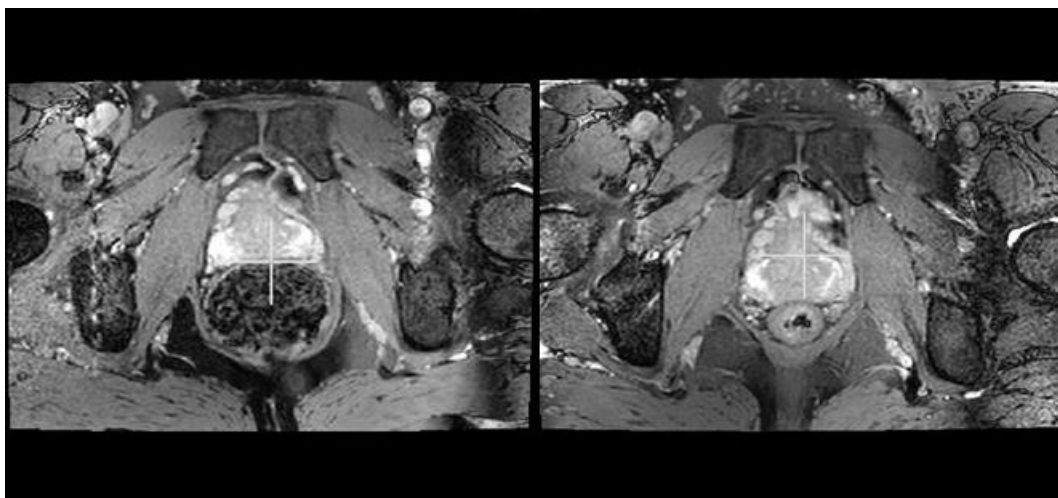
The lack of correlation between prostate and SV inter- and intra-fractional motion has implications for the use of prostate tracking devices, such as calypso transponders, when simultaneously treating the SV. Caution must be employed when considering reducing treatment margins on the basis of an assumed confidence about exact CTV location.

## Contributing factors to prostate motion

### Rectal and bladder volumes

Rectal distension is a major contributor to, and correlates with, prostate motion (**figure 2**). This likely relationship was identified in some of the earliest prostate motion analyses [96, 97] and subsequent studies have confirmed this association particularly in relation to AP translation and rotation around the prostate apex [54, 55, 57, 98-100].

This relationship has also been demonstrated with MRI. A small study of seven patients measured the prostate midpoint relative to bony anatomy on pre and post treatment MRI and found variation in rectal filling that correlated strongly with anterior displacement and a lesser correlation between bladder filling and superior motion [56]. A larger study of 42 patients used cine-MRI scans every nine seconds for nine minutes at baseline without any bowel preparation, before CT planning with bowel preparation and at a random point during RT with bowel preparation [58]. This demonstrated rectal gas and stool to be responsible for 74% of identified > 3mm prostate motion. Despite this voiding prior to imaging and bowel preparation did not significantly reduce intra-fraction motion.



Rectal diameter may have a threshold above which its effect on prostate motion becomes more significant. It has been suggested that maximum rectal diameters above 3.5 - 4.5 cm or mean cross sectional areas  $\geq 9.5 \text{ cm}^2$  at planning imaging are predictive of significant variation in rectal size and prostate position during therapy[101-103].

The increased motion associated with initial large rectal volumes may also negatively influence treatment outcome. In one series of 127 patients those with a mean rectal cross sectional area greater than the group average of  $11.2 \text{ cm}^2$  at the time of planning experienced greater biochemical failure rates (HR 3.89) and more toxicity from treatment [104]. Another study examined outcomes for 549 patients, stratified by anorectal volumes  $\geq 90 \text{ cm}^3$  at time of planning CT, and found that in

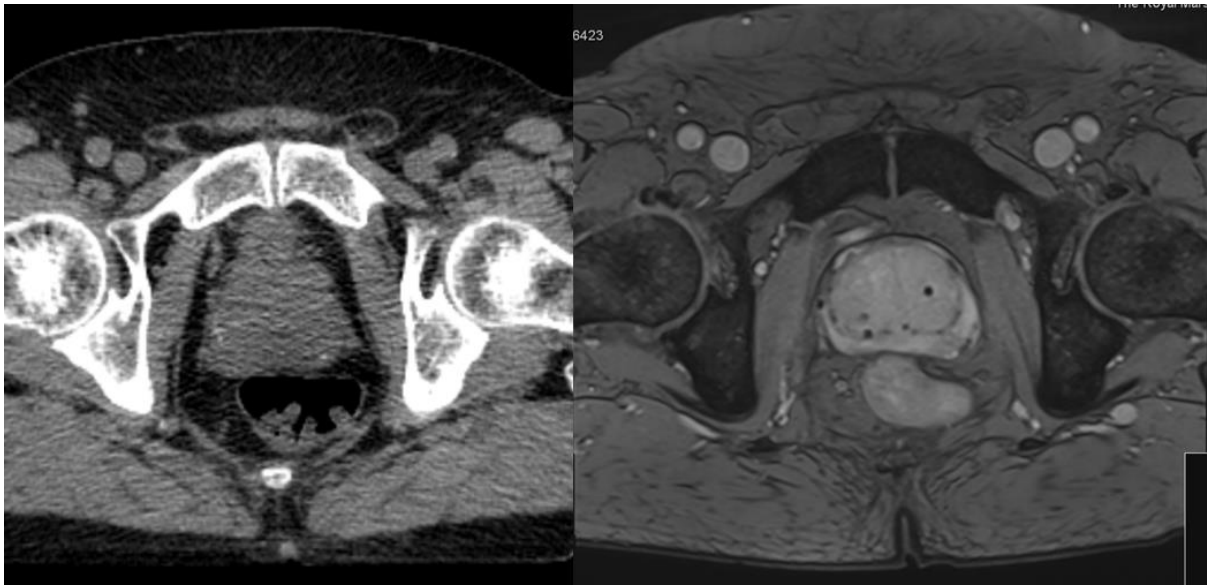
patients with a risk of SV involvement >25% those with a larger rectal volume had a 15% reduction in freedom from failure at five years ( $p=0.01$ ) [105].

Various approaches such as diet modification, bowel regimens (enemas, laxatives, etc.) and immobilizing endorectal balloons have been used in an attempt to reduce rectal variation. The evidence for efficacy of these techniques is mixed and a recent systematic review concluded that it was impossible to recommend one particular interventional strategy with further prospective studies required [106]. The use of effective daily image guidance may mitigate any effects of initial rectal distension.

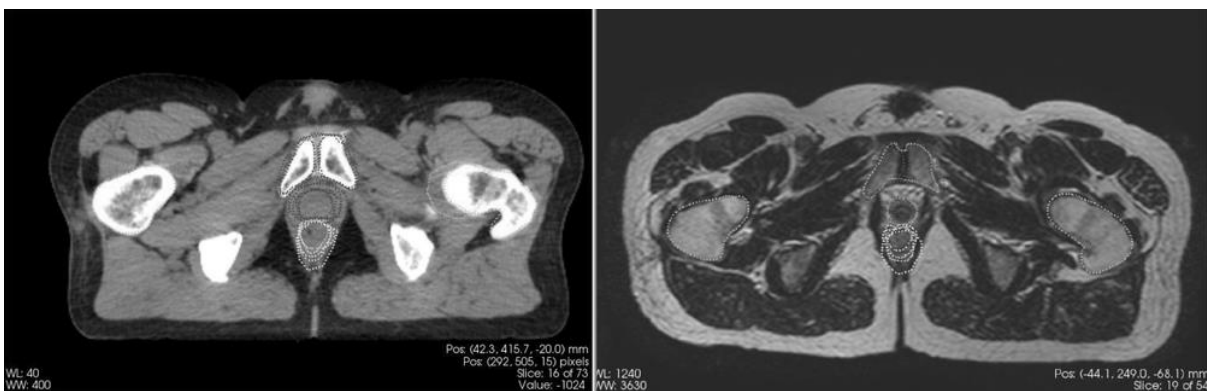
Although the potential effect of rectal volume on prostate motion appears clear, the effects of changes in bladder volume appear at most to be minimal. Various studies have provided some limited evidence suggesting a weak relationship between the two [30, 56, 100, 107] but other groups have failed to find any association [108-111]. It would therefore seem likely that simple bladder filling protocols are sufficient to minimise any bladder volume effects. However, for prone patients or patients with restricted abdominal movement, e.g. due to MR coils, bladder filling may affect prostate motion and such setups should be avoided.

#### Target delineation

Inter- and intra- operator variation in target delineation, particularly at the SV and apex, can be significant [49, 112, 113]. This is in part due to poor soft tissue definition on CT imaging making identification of the boundaries of the prostate challenging. It is known that CT delineated prostates are routinely larger than the true anatomical site. One study comparing the CT delineation by six radiation oncologists with photographic anatomical images found that the contoured prostate was on average 30% larger than the true gland but only included 84% of its volume, such that posterior portions were always missed and anterior normal tissue always included [114]. MRI provides better distinction between adjacent soft tissue structures and has been shown to be superior at identifying the prostate apex, SV and posterior border (**figure 3**). Multiple studies have demonstrated a reduction in volume of contoured prostate, of between 30-35% in the three largest series, when MR imaging is used to provide additional information for planning [115-117]. These reductions are primarily due to reduced variation at the superior and inferior extent of the prostate and translate into reductions in delivered dose to the rectum [117-120].



This improved soft tissue visualisation on MRI has also been shown to reduce intra- and inter-observer variation in prostate contouring (**figure 4**) [115, 121]. Using MRI in combination with an education program it may be possible to reduce this inter-observer variation further [122]. A final benefit from use of MRI for prostate delineation comes from the reduced metal artefact degradation from prosthetic hips which may significantly affect CT imaging and subsequent contour consistency [123]. Good correspondence with MR imaging and prostatectomy specimens has been shown with a correlation coefficient of up to 0.86 [124, 125].



Therefore it appears MR-based contouring of the prostate can be done more consistently and with higher fidelity than CT, leading to reduced treatment volumes and radiation to surrounding structures.

Recently work has focused on the use of multi-parametric (MP) MR to identify areas of high grade tumour within the prostate gland [126]. The use of modelling for voxelwise prediction of disease presence on MR imaging has been shown to have promise [127]. Confident identification provides the potential to focus dose intensification to this region, which may be the most likely site of ultimate disease recurrence [128]. MPMR guided targeted dose escalation is the subject of the ongoing phase III FLAME study and results are awaited with interest [129]. It has been shown that the dominant lesion within the prostate can be reliably identified on MP-MR but as yet data on how this region may be affected by prostatic deformation during therapy is scarce and requires future work [130]. In a study using collimator adjustments to account for prostate rotations, patients with

and without focal boost were equally sensitive to rotations, indicating a limited effect of prostate rotations on boost dose [131].

### Adaptive radiotherapy for inter-fraction motion

The current standard practice to manage inter-fraction variations is to use IGRT by repositioning the patient based on the rigid-body registration of the planning image and the image of the day acquired just before treatment, followed by delivery of the original (unchanged) plan. IGRT addresses the translational motions, including set-up errors, but cannot completely account for the organ deformation, rotation, and independent motion between different organs. The ideal method to fully account for the inter-fractional variations is to adapt the treatment plan based on the anatomy of the day. Such adaptive planning process may be performed in an online or offline manner [132, 133]. The offline adaptive process, i.e. using the information from previous treatments to provide feedback for future deliveries, has been used to correct systematic, predictable variations [45, 134, 135].

Online adaptive radiotherapy (ART), on the other hand, is capable of addressing both systematic and random variations and is the most effective strategy for precisely irradiating concurrent targets that move independently. Online planning must be fast enough to be completed within a few minutes while the patient is lying on the table waiting for treatment. Although such fast planning is generally challenging using conventional planning technologies, adaptive re-planning does not need to start completely from scratch. For example, it can start with an initial plan fully optimized from the planning images for the same patient and adapt for the anatomy of the day ('warm start' optimization). Technologies to facilitate this, such as the quality of in-room imaging, image registration and segmentation, plan optimization algorithm and computing hardware, are advancing significantly and rapidly. For example, integration of diagnostic-quality MRI in the treatment room, graphic-processing unit (GPU) accelerated auto-segmentation and dose calculation, rapid plan modification algorithms, and plan adaptation based on previous knowledge or a previously-created plan library are among the technology advances that can speed up adaptive planning significantly. In particular, among a number of online planning algorithms [136-139], an online adaptive planning scheme [138] has been developed that features two distinct steps: a) segment aperture morphing (SAM), and b) segment weight optimization (SWO), and has been used for prostate cancer [140]. It has been demonstrated that the online SAM+SWO scheme can adequately account for all inter-fraction variations and can be completed within 10 minutes for prostate RT [140]. Alternative techniques for ART of prostate cancer are reported [141-144] and reviewed previously [145, 146].

With online ART, a CTV-PTV margin can reach as low as 3 mm, depending mainly on intra-fraction variations. Such a small margin would be highly desirable to reduce treatment-related toxicities and/or to allow dose escalation. Online ART is particularly important for hypo-fractionated RT or SBRT where the penalty of a geographical miss and/or over dosing of normal tissue for a single fraction is significant. However, with such small margins, target definition accuracy becomes much more critical to avoid the risk of compromising clinical outcome [147]

## MRI-guided adaptive radiotherapy for inter- and intra-fractional motions

The high soft tissue contrast makes MRI an ideal imaging modality for online ART. MRI-guided RT delivery systems that integrate MR scanners with radiation delivery machines are being introduced into the clinic [148]. For example, ViewRay system (Oakwood Village, OH) combines a 0.35 T MRI scanner with three  $^{60}\text{Co}$  sources with multi-leaf collimators (MLC). Integration of a diagnostic MRI scanner with a Linac (MR-Linac) is also under development. The MR-Linac proposed by Lagendijk et al at the University Medical Center Utrecht [149] that integrates a 1.5 T MRI scanner with a 6 MV Linac is being developed for commercialization [7]. With CT based IGRT, image quality adversely affects the CTV-to-PTV margins required for targeting and ART, mainly due to the residual uncertainties from the soft-tissue contrast for the image modality [150]. It is anticipated that the residual uncertainty with diagnostic quality MRI will be drastically smaller than those with CT or CBCT, allowing a smaller CTV-to-PTV margin.

The design of the MR-Linac system comprises a 6 MV Linac (Elekta Inc) mounted on a ring around a modified 1.5 T MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) and an online ART planning system [7]. The system is designed to be able to simultaneously image and irradiate the patient. The radiation beam is shaped by a 160-leaf MLC system and travels through the closed-bore MRI before it enters the patient. The accelerator and MRI are designed to be magnetically decoupled so that the MR images are not distorted by the presence of magnetized accelerator components, and the operation of the accelerator is not hampered by the magnetic field. A series of MR sequences can be scanned to produce pre-, during- and post-treatment images. Once the MR-Linac is fully developed, the pre- and post-treatment MRI can include both morphological (T1, T2...) and functional (DWI, DCE etc.) images. The during-treatment MRIs include cine MRI (2D), morphological 3D (e.g., T1, T2) and 4D images.

The online planning system integrated in the MR-Linac should be designed to generate an adaptive plan based on the pre-treatment MRI in the following steps: 1) deformably register the pre-treatment MRI with the planning images, 2) rapidly generate a plan by modifying or re-optimizing the original plan or by fast adaptive re-planning to account for the different anatomy based on the registered images, and 3) quickly perform a software-based QA check on the new plan. To be successful the system should complete this 3-step online process within 5 minutes while the patient is still lying on the couch. Then, the new adaptive plan is delivered simultaneously with the during-treatment images acquired.

The MR-Linac system is designed to be able to track/monitor organ (e.g., prostate gland) motion in real-time on 2D (cine) MRI during the radiation delivery. Because of superior soft tissue contrast, this tracking should be very accurate and effective. The radiation beam can be paused, via the capability of exception gating, if prostate motion is detected outside a pre-defined range, and can be resumed if the prostate moves back to the range. Alternatively, it is anticipated that with technical enhancements, the radiation beam may be dynamically shaped to trace the prostate motion detected from the cine MRI acquired on the plane perpendicular to the beam orientation. Either way, the intra-fractional variations can be managed effectively, thus the margin required to account for intra-fraction variation can be reduced.

The superior soft tissue contrast along with function/physiological information with MRI will significantly improve the performance and implementation of the online ART strategy (e.g.,

improved target definition, image registration, auto-segmentation). In addition, with the availability of real-time MR imaging during RT delivery to measure and monitor intra-fraction motion, the motion management techniques (gating or tracking) can be improved. With both inter- and intra-fractional variations being accounted for, the CTV-to-PTV margin may be safely reduced to  $\leq 3$  mm. Because the PTV often overlaps with rectum and bladder, such a drastic reduction in PTV margin should reduce toxicities or allow RT doses to be safely escalated to eradicate the tumour, thus improving treatment outcomes.

## Conclusion

Extensive literature demonstrates that substantial inter- and intra-fractional variations occur in radiation therapy for prostate cancer. These variations include translational and rotational motions, deformations, and independent motions between the structures, and consist of both random and systematic components. While the current standard practice of IGRT based on CT or CBCT can only address translational motion, adaptive radiotherapy has the potential to fully account for these variations. The superior soft-tissue contrast and the continuous imaging capability of MRI are highly desirable for the management of inter- and intra-fraction variations. Integration of MRI radiotherapy delivery and ART capability, such as with the MR-Linac, holds the promise to optimize radiotherapy to the prostate. Using this approach the improved delineation of target and OARs in both planning and delivery, will mean inter- and intra-fractional variations may be confidently accounted for, permitting use of a decreased CTV-to-PTV margin.

Conflict of Interest:

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## Legend

**Table 2: Inter-fraction systematic and random motion**

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**Table 3: Studies of intra- and inter-fraction rotation**

**Figure 1: Inter-fraction prostate, rectum, and bladder motion measured on repeat CT imaging**

**Figure 2: Effect of rectal filling on prostate position**

**Figure 3: Axial MR and CT imaging of the prostate**

**Figure 4: Prostate apex contoured by multiple operators on MR and CT images**